45-Year-Old Man with Leg Pain and Numbness

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Case Description

A 45-year-old man presents with a 5-day history of right leg pain. He describes the pain as acute in onset with constant numbness with overlying pins and needles burning involving his anterior shin. He has noticed that the toes on his right foot have been dragging on the floor, causing him to trip. One day prior to presentation, he developed similar but milder symptoms on his left leg. He denies history of low back pain, trauma, rashes, joint pain, constitutional symptoms, polydipsia, polyuria, or history of hepatitis. There is no history of prolonged kneeling, squatting, leg crossing, or prolonged immobility. He has no medical problems, takes no medications, and has no family history of neurologic problems. He does not use any tobacco, alcohol, or any illicit substances.

His general examination reveals intact peripheral pulses and no joint swelling nor decreased range of motion. His strength examination is notable for right foot weakness in dorsiflexion and eversion, with preserved strength of foot inversion, knee flexion and extension, and hip abduction. His sensory examination reveals diminished sensation over the anterolateral shin and dorsum of the foot, sparing high thigh or posterior lower leg. There are similar but milder examination findings on his left leg. There are no asymmetries in reflexes and his plantar responses are downgoing. He walks with a steppage quality to his gait on his left.

What Is Your Preliminary Diagnosis?

The differential diagnosis for unilateral leg pain is broad and can be divided into neurologic and non-neurological disorders. A thorough history and examination are essential to narrow down such a broad differential. A history needs to include the onset and progression of symptoms, location, presence of numbness or weakness, and aggravating or alleviating factors. Assessment of comorbid medical conditions such as diabetes, alcohol use, infections such as hepatitis, travel history, and family history of neuropathy are useful. The presence of rash, weight loss, and constitutional symptoms is also helpful. Non-neurologic disorders, such as bursitis, peripheral vascular disease, fibromyalgia,

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and other musculoskeletal causes, can be considered initially in this patient prior to the history. As this patient has signs suggestive of focal neuropathic pain, sensory loss, and asymmetric foot drop, the diagnosis appears most consistent with neurologic causes.

The next step in diagnosis involves the physical examination. A general examination, including examination of skin for rashes, joint examination, and presence of peripheral pulses, can also provide additional diagnostic clues. A focused neurologic examination is needed if a neurologic cause is suspected, including strength examination, sensory examination, deep tendon reflexes, and observation of gait.

Prior to examination, his differential diagnosis for a neurologic cause of leg pain and foot drop depended on the area of the nervous system involved. The absence of upper motor neuron signs (increased tone, hyper-reflexia, and upgoing plantar response), a sensory level, and bowel/bladder involvement suggests that the site of the lesion is at or distal to the anterior horn cell of the spinal cord. The presence of sensory symptoms excludes pure motor disorders such as motor neuron diseases, neuromuscular junction, or muscle disorders. The most probable site of disease is at the nerve roots, plexus, or peripheral nerves.

Atypical L5 radiculopathy could cause pain in this distribution, but it is classically associated with intermittent radiation and back pain. Disc herniation, spinal foraminal stenosis, mass lesions, infections (such as Lyme disease or tuberculosis), or inflammatory conditions, such as sarcoidosis, are potential considerations for a radiculopathy. Similarly, causes of a lumbosacral radiculoplexopathy were possible, such as structural lesions, diabetic amyotrophy, and non-diabetic lumbar radiculoplexopathy. However, absence of findings suggesting multiple nerve root involvement within the same limb, such as involvement of proximal muscles or calves, makes this less likely.

The motor examination narrows down the differential diagnosis considerably. It is important to perform a neurologic examination as to avoid unnecessary testing, interventional procedures, and even surgery [1]. Attention can be paid to his strength and sensory examination, particularly asymmetry in testing. The presence of weakness in foot dorsiflexion and ankle eversion indicates involvement of the peroneal nerve. However, preserved strength of ankle inversion, knee flexion, or hip abduction shows integrity of more proximal tibial, sciatic, and superior gluteal nerves, respectively. This examination is suggestive of a common peroneal nerve neuropathy, and the sensory examination is also consistent with this conclusion.

An approach to evaluating a patient with suspected polyneuropathy is demonstrated in Fig. 32.1. Characterizing the patient's symptoms can help diagnose and characterize different types of polyneuropathy, which can inform further testing to refine the differential diagnosis. One should first characterize whether the symptoms are sensory, motor, autonomic, or a combination of these. In addition, the pattern of involvement, onset, and progression of symptoms can suggest categories of causes of symptoms. Finally, as one would do for the evaluation of polyneuropathy, inquiring about red flags associated with atypical causes is necessary. These are also listed in Fig. 32.1 and include acute or subacute onset, relapsing or remitting course, marked asymmetric pattern of pain, concomitant cranial nerve deficits, and upper extremities being more severely affected than lower extremities. The presence of these could suggest immune-mediated, vasculitic, neoplastic, or paraneoplastic causes. The presence of these historical signs in a neuropathy, rather than a radiculopathy, should lead to prompt neurological referral and additional investigations, including electro-diagnostic testing and serology. Lumbar puncture, expanded serologic evaluation, and a potential nerve or muscle biopsy are possible additional considerations.

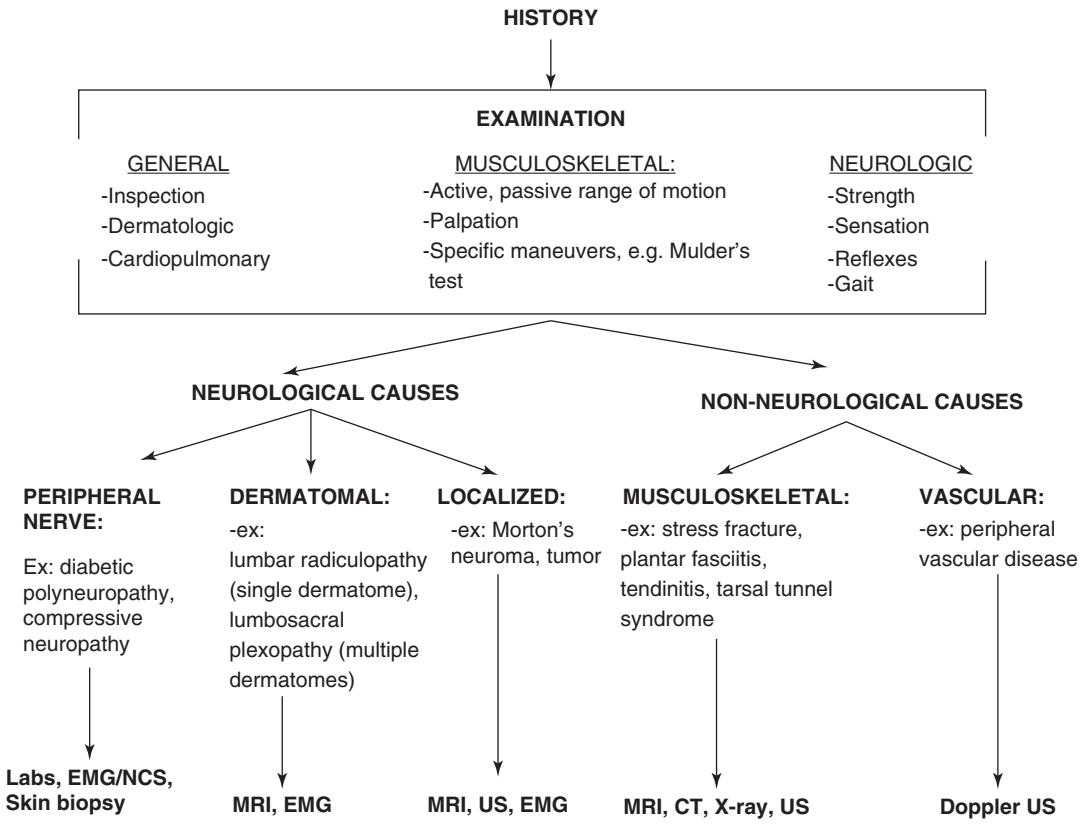

Fig. 32.1 Approach to polyneuropathy

This patient's history and examination is suggestive of asymmetric bilateral peroneal neuropathy, with features suggestive of an inflammatory cause such as mononeuritis multiplex. Further diagnostic testing will be needed to determine the cause. A list of diagnostic considerations for asymmetric or the beginning of a multifocal neuropathy is listed in Table 32.1.

How Is Diagnosis Confirmed?

The differential diagnosis based on this patient's history is confirmed by pertinent diagnostic testing. Imaging of the affected extremity, such as an MRI, is an option should a structural cause be suspected. Electro-diagnostic testing, including electromyography and nerve conduction studies with an experienced provider, is necessary to confirm and characterize the diagnosis of nerve pathology. It allows insight into the severity of the process and whether the process is primarily related to axon degeneration or peripheral demyelination. Findings of demyelination are not consistent with vasculitic neuropathy. This information further informs the likelihood of certain diagnoses, as well as prognosis and timing of treatment. Initial evaluation and selected additional labs to consider are listed in Table 32.2. Given the morbidity associated with systemic vasculitis, as well as its long-term treatment with immunosuppressant, nerve/muscle biopsy is important for definitive diagnosis

Table 32.1 Differential diagnosis of asymmetric or multifocal neuropathy [30, 31]

1. *Vascular/ischemic*	3. *Mechanical*
Vasculitis	Multiple injuries or burns
Primary systemic vasculitis	Entrapment syndromes
Microscopic polyangiitis	Wartenberg's migratory sensory neuritis
Polyarteritis nodosa	4. *Infections*
Granulomatosis without polyangiitis	Viral disease: HBV[a], HCV[a], HIV[a], VZV, CMV[a], WNV, HTLV-1[a]
Granulomatosis with polyangiitis	Lyme disease[a]
Eosinophilic granulomatosis with polyangiitis	Tuberculosis
Essential mixed cryoglobulinemia	Leprosy[a]
Vasculitis secondary to other connective tissue disorders	Other
Rheumatoid arthritis	5. *Neoplastic*[a]
Systemic lupus erythematosus	Direct infiltration
Sjogren's syndrome	Paraneoplastic syndromes
Systemic sclerosis	Tumor compression
Dermatomyositis	Primary AL amyloidosis
Mixed connective tissue disease	Intravascular large B-cell lymphoma
Hypocomplementemic urticarial vasculitis syndrome	Lymphomatoid granulomatosis
Non-systemic vasculitides	Acute leukemia
Non-systemic vasculitic neuropathy	6. *Genetic*
Diabetic radiculoplexus neuropathy	Charcot Marie Tooth variants
Localized cutaneous or neuropathic vasculitis	Krabbe disease
Sickle cell anemia	Tangier disease
Thrombophilic or hemophilic states	Porphyria
Idiopathic thrombocytopenic purpura	Hereditary neuropathy with liability to pressure palsies
Embolic causes	Mitochondrial disorders
Cholesterol emboli	Familial amyloid polyneuropathy
Atrial myxoma	7. *Drug-induced*[a]
Infective endocarditis	Antibiotics: penicillin, sulfonamides, minocycline
2. *Inflammation/Immune-mediated*	Interferon-alpha
Sarcoidosis[a]	TNF-alpha inhibitors
Behcet's disease[a]	Montelukast and leukotriene receptor antagonists
Guillain-Barre variants	Amphetamines
Multifocal motor neuropathy	Cocaine
Lewis-Sumner syndrome	Heroin
Inflammatory bowel disease[a]	Others
Other	

[a]Occasionally associated with vasculitis

in the evaluation of a suspected vasculitic neuropathy.

In this case, electro-diagnostic testing performed in the patient showed findings consistent with moderate-to-severe asymmetric bilateral axonal peroneal neuropathies, left worse than right, raising concern for a mononeuritis multiplex pattern. Initial workup showed normal hemoglobin A1c, elevated erythrocyte sedimentation rate and C-reactive protein, a negative antinuclear antibody, negative hepatitis B and C testing, negative rheumatologic markers, and otherwise unremarkable labs. A nerve biopsy was ultimately pursued, which demonstrated

Table 32.2 Laboratory and imaging evaluation when immune-mediated neuropathy is suspected [30, 31]

Routine	Second line
Complete metabolic panel (electrolytes, urea, creatinine, liver function tests)	Anti double-stranded DNA antibody, anti-Smith antibody, cyclic citrullinated peptide antibodies
Complete blood cell count (for anemia or eosinophilia)	Sinus X-ray
Serum protein electrophoresis	Chest CT
Urine protein electrophoresis	Anti-SSA/SSB, Schirmer test
Hemoglobin A1c or 2-hour glucose tolerance test	Angiotensin-converting enzyme level
Chest X-ray	Porphyria screen
Erythrocyte sedimentation rate, C-reactive protein	HIV, West Nile virus, Lyme disease, cytomegalovirus
Hepatitis B and C serologies	Lumbar puncture and CSF analysis
Antinuclear antibody, antineutrophil cytoplasmic antibody, rheumatoid factor	Paraneoplastic antibodies
Cryoglobulins, C3, C4	Imaging for malignancy

mononuclear inflammatory cells with associated fibrinoid necrosis of the vessel wall consistent with vasculitic neuropathy. After rheumatologic consultation, it was determined that there was no other organ involvement and he did not meet diagnostic criteria for polyarteritis nodosa or other systemic vasculitides. Therefore, his diagnosis was determined to be mononeuritis multiplex as a consequence of non-systemic vasculitic neuropathy.

What Is the Pathophysiology of This Condition?

The pathophysiologies of immune-mediated neuropathies are varied, as are those of the different vasculitides. Vasculitis as a disorder can be either systemic, affecting multiple organs, or localized to the nervous system. When neuropathy occurs in absence of a systemic vasculitis, this is referred to as non-systemic vasculitic neuropathy (NSVN). NSVN is the most commonly reported vasculitic neuropathy [2–4]. Systemic vasculitis can be a primary disorder, related to inflammation of small, medium, or large blood vessels. For example, neuropathy can affect 60–70% of patients with polyarteritis nodosa and eosinophilic granulomatosis with polyangiitis, whereas it can affect 40–50% of patients with microscopic polyangiitis [5]. In addition, vasculitis can be secondary as a result of infections, drugs, and cancers. No specific trigger can be found for some.

Primary vasculitic neuropathies represent a group of heterogeneous disorders, each with different mechanisms that may not be completely understood for each disease. For example, microscopic polyangiitis and non-systemic vasculitic neuropathy are caused by separate mechanisms involving anti-neutrophilic antibodies and complement pathways, respectively [6]. Whether immune complex deposition in vessel walls leads to an inflammatory cascade, or cell-mediated immunity by T-cell pathways leads to vessel wall injury, the final common pathway leads to ischemic injury of nerves. Damage of the vasa nevorum, particularly epineurial arteries, leads to ischemic injury and resultant degeneration of axons [7].

How Is This Problem Managed?

The primary focus of treatment in immune-mediated (including vasculitic) neuropathy is based on treating underlying inflammation. Treatment of other primary systemic vasculitides is used to guide treatment based on paucity of randomized clinical trials for NSVN. This often involves immunosuppressive agents such as glucocorticoids, cyclophosphamide, rituximab, azathioprine, and methotrexate. The approach to treatment, including in NSVN, involves two phases. First, remission-induction

therapy is meant to stop inflammatory damage from continuing acutely to sub-acutely, usually with corticosteroids. This can be accomplished with monotherapy of prednisone 1 mg/kg daily with prolonged taper. Combination therapy with a second agent, such as azathioprine or mycophenolate mofetil, can also be used for additional effects seen later in the course on induction and remission. The choice of whether to use a second agent in the acute phase depends on the severity of disease. For example, less intense agents such as methotrexate or mycophenolate mofetil can be added for milder cases, and plasma exchange can be substituted in for severe cases [8].

After induction therapy, maintenance therapy involves continued treatment with these medications for at least 18–24 months with the aim of reducing the likelihood of clinical relapses. Escalation in the intensity of regimen (such as addition of plasma exchange, IVIG) is guided by the initial severity as mentioned previously, or also the response to less intense therapy. Treatment with maintenance immunosuppression with tapering corticosteroids and a second agent (azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide, etc.) is continued until remission has been achieved. If there is associated hepatitis B or C infection, treatment with antivirals is warranted, with timing of treatment determined on a case-by-case basis.

Multidisciplinary teamwork between neurology and rheumatology is important in vasculitic neuropathy. Management of immune-mediated neuropathy is focused on supportive care as well as its underlying cause. Physical and occupational therapy is helpful for recovery in presence of sensory and motor deficits. Management of analgesic treatment is warranted for pain associated with vasculitic neuropathy. Several medication classes are options for pain control, including anticonvulsants, tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and opioids, which are to be discussed later in this chapter. It is important to note that symptomatic treatment of pain in these conditions is often not based on large, randomized controlled trials for each separate disease process resulting in neuropathy. Instead, symptomatic treatment of pain is often borrowed by successful treatments in studies dominated by more common neuropathic pain conditions such as painful diabetic neuropathy or post-herpetic neuralgia [9–11]. Please refer to prior chapters on diabetic neuropathy for further information.

As mentioned previously, the strength of evidence for treatment specific to NSVN is suboptimal. More importantly, it is worth noting that these trials for primary systemic vasculitides are often not focused on neuropathy or appropriate measurements of efficacy in neuropathy. Therefore, their efficacy is extrapolated for vasculitic neuropathy and cannot be definitively relied on [12]. Consultation with a rheumatologist or neurologist is warranted in immunosuppressant management.

In summary, treatments are often individualized based on disease process, severity, and patient factors. Either corticosteroid monotherapy or combination with another immunosuppressive agent is used in a higher dose induction phase, followed by tapering doses over a maintenance period. Urgent consultation for treatment regimens with rheumatology or neurology is warranted based on the organ systems involved.

What Is the Prognosis of This Condition?

The prognosis of a neuropathy depends on its cause and its mechanism. As a general principle, nerve injury resulting in axonal damage has a longer recovery time than damage from demyelination. As vasculitic neuropathy is axonal in

nature, this underscores the need for prompt diagnosis and treatment to mitigate damage with prolonged consequences.

NSVN rarely spreads beyond the peripheral nervous system to other organs. The relapse rate is estimated to be 30% after treatment is started [13]. The prognosis is good in those who receive treatment. In a cohort study, approximately 13% of treated patients become asymptomatic, and 68% have mild or moderate symptoms while remaining independent and ambulatory [14]. Mortality is noted to be approximately 10% at 5 years [14]. Chronic pain is common and ranges from 37 to 60% of patients who are treated [14, 15].

Discussion

Prevalence

The epidemiology of NSVN is poorly studied, but it can be estimated based on studies of systemic vasculitides. The annual incidence of primary and secondary vasculitis was 140 cases per million people in a Spanish study. Primary systemic vasculitis represented 82 percent of these cases, [16] with the most common secondary vasculitis resulting from connective tissue disease. A separate Parisian study estimated the prevalence of individual primary systemic vasculitides, finding a range from 10 to 31 per 1,000,000 adults for each disease process [17]. For example, most common disease was polyarteritis nodosa, with prevalence of 30 per 1 million, followed by microscopic polyangiitis.

These studies do not account for the prevalence of neuropathy in these patients. Neuropathy is a common manifestation of some primary and secondary vasculitides. As an example, it occurs in approximately 74% of PAN patients, [18] most commonly resulting in a mononeuritis multiplex pattern. The most common vasculitic neuropathies include NSVN, microscopic polyangiitis, and polyarteritis nodosa [2]. It is not uncommon for painful asymmetric neuropathy to be a presenting symptom for these disorders and the majority of presentations of NSVN. [14]

Differential Diagnosis

The use of the history and physical is important to accurately determine whether symptoms are related to a polyneuropathy, mononeuropathy, radiculopathy, or other neurologic process. The differential for polyneuropathies and radiculopathies is beyond the scope of this chapter. A differential diagnosis for asymmetric or multifocal neuropathy is listed in Table 32.1.

Compressive or multifocal mass lesions or burns should not be missed on history or diagnostic testing. Non-compressive causes can result from inflammation, infection, degeneration, and infarction. A more detailed list of diagnostic considerations for asymmetric or multifocal neuropathies is listed in Table 32.1. Underlying diabetes, gammopathies, or alcoholism can result in asymmetric nerve dysfunction, but more classically causes a distal, symmetric polyneuropathy. Non-compressive causes can also result from inflammatory insults such systemic vasculitides. Primary vasculitic disorders associated with neuropathy include polyarteritis nodosa, microscopic polyangiitis, ANCA-associated vasculitis, among others. Systemic vasculitides can also result secondarily from connective tissues disease (such as rheumatoid arthritis or systemic lupus erythematosus), sarcoidosis, infections, drugs, or malignancy. Finally, non-systemic vasculitis of the peripheral nervous system is a syndrome with peripheral nerve vasculitis without clinical or laboratory evidence of another systemic vasculitis. Diabetic neuropathic injury, if asymmetric, classically results in an asymmetric radiculoplexus neuropathy, but it can rarely cause

individual nerve injury. Once considered a separate entity, diabetic radiculoplexus neuropathy (also known as diabetic amyotrophy) is classified as a form of NSVN.

It is worth noting that an acute or subacute mononeuropathy can sometimes be the initial phase of mononeuritis multiplex, a syndrome that requires an expedited evaluation to reveal the underlying cause, many of which are listed in Table 32.1.

Predictive Value of Different Clinical Features (Both on History and Physical Exam) and Lab Testing/ Imaging

Neuropathy secondary to vasculitis presents focally (over a peripheral nerve distribution) and painfully over an acute to subacute time period. There have been limited studies, often small case-control or retrospective cohort studies, which have addressed predictors of a vasculitic neuropathy. For example, pain is a particularly sensitive finding in vasculitic neuropathy, which occurs in 90% of patients [14]. Rapid onset, defined as symptom onset less than 1 month from biopsy, was poorly sensitive and 100 percent specific in one small retrospective study of 40 patients [19].

The most common pattern of involvement is classically mononeuritis multiplex (multiple mononeuropathies), but plexopathy and distal sensorimotor polyneuropathy can also occur. Asymmetry or multifocal involvement (either clinically or by electrodiagnostics) is common due to characteristic patchy involvement and is one of the more specific characteristics [20–22]. However, due to varying EMG definitions and small sample sizes, precise estimates of specificity are difficult to assess. In addition, as the neuropathy progresses and more nerves are affected, the overall pattern may look similar to a distal length-dependent polyneuropathy.

Just as clinical and electrophysiological data is not completely sensitive or specific to vasculitic neuropathy, laboratory data also has considerable overlap with other diagnoses. Elevated erythrocyte sedimentation rate and C-reactive protein were studied in two small studies and were at least sensitive for vasculitis, although they were not specific to this diagnosis [19, 23]. In addition, this does not distinguish between causes of vasculitic neuropathy, other neuropathic disorders that would result in elevated markers, and elevation due to other chronic conditions. No other laboratory or radiographic findings have been studied that have reliable predictive value for NSVN. There are additional clinical and laboratory data that, conversely, have low association with NSVN and systemic vasculitic neuropathy. These include demyelination, CSF pleocytosis, CSF protein >110 mg/dL, and pure motor symptoms [24].

Arguably the most important diagnostic test is the nerve and muscle biopsy. One cohort study of 70 combined superficial peroneal nerve (SPN) and peroneus brevis muscle (PBM) biopsies classified biopsy samples as positive, suspicious, or negative for vasculitic neuropathy. A positive SPN/PBM biopsy had 60% sensitivity for vasculitic neuropathy, while the group of positive or suspicious biopsies had a 86% sensitivity and 85% specificity [25]. The yield of sural nerve biopsy is less robust, [26] perhaps related to this nerve being less involved in vasculitic neuropathies. The combined nerve and muscle biopsy has also been questioned in terms of its yield over nerve biopsy alone [4, 25]. It is worth noting that these studies are not specific to NSVN and, therefore, the exact sensitivity for biopsy in NSVN can only be estimated imprecisely, some suggest approximately 50% [13].

While the sensitivity and specificity of biopsies are imprecise, the diagnosis of vasculitic neuropathy often relies upon the use of histopathologic data to establish high confidence in diagnosis according to the Brighton Collaboration group [27]. In the absence of a classic clinical presentation with either classic electrodiagnostic or clinical exam findings, a biopsy is essential for diagnosis.

Strength of Evidence for Different Treatment Modalities

As previously mentioned, the evidence for specific treatments for NSVN is largely based on data from treatment of systemic vasculitis, although studies did not have reliable outcome measures for neuropathy or pain. Therefore, it is difficult to accurately extrapolate the quality of evidence for vasculitis confined to the peripheral nervous system.

Regarding analgesic treatment, evidence for specific agents can be borrowed from trials in more common neuropathic pain conditions, such as diabetic neuropathy or post-herpetic neuralgia. These medications include SNRIs, TCAs, anticonvulsants, and consideration of opioid agents with consideration of risks and benefits. Discussion of the level of evidence supporting these agents can be found in a separate chapter on diabetic neuropathy.

As mentioned previously, treatment regimens for vasculitic neuropathy utilize corticosteroids with or without a second immunosuppressive agent, such as cyclophosphamide, rituximab, mycophenolate mofetil, or others. Specific regimens can be customized to each individual patient and disease process, which is beyond the scope of this chapter. Rheumatologic or neurologic consultation is warranted for creating treatment regimens.

Recognizing the heterogeneity of disease processes, treatment regimens, and strength of evidence surrounding each, in this case of NSVN, immunomodulatory treatment is unsurprisingly without strong evidence for specific regimen. A 2007 Cochrane review of immunosuppressive treatment of non-systemic vasculitic neuropathy found no adequate randomized controlled trials [28]. Two retrospective cohort studies have analyzed corticosteroid monotherapy versus corticosteroid plus second-line therapy [14, 29]. One study demonstrated that combination (cyclophosphamide plus steroid) therapy was more effective than corticosteroid monotherapy in achieving sustained improvement at 6 months in a cohort of 48 NSVN patients [14].

Future Directions or Clinical Trials in Progress

Future study is warranted on specific treatment regimens for specific vasculitic disease entities, although the prevalence of individual disorders makes design of studies challenging. Registries, such as one from the UK and Ireland Vasculitis Study group, can be useful in the study and understanding of these disorders and their treatments. Research continues to focus on the pathogenesis of NSVN as it compares to other organ vasculitides.

Conclusion/Summary

Non-systemic vasculitic neuropathy is an isolated vasculitis of the peripheral nervous system. It is the most common of the vasculitic neuropathies, which often results in asymmetric, painful sensorimotor deficits. History of asymmetry, rapid progression, or other red flags could suggest a vasculitic process, which could result in significant morbidity if left untreated. It is paramount to evaluate if an underlying systemic vasculitis is contributing to avoid damage to other organ systems.

Diagnosis is based on history and exam findings, supported by laboratory data, and often needs confirmation by nerve biopsy. The prognosis of vasculitic neuropathy depends on the underlying cause and chronic pain is common. Control of neuropathic pain is possible with the similar agents as other neuropathic pain (TCAs, anticonvulsants, SNRIs), with consideration of opioids in select cases. In addition, control of inflammation with corticosteroids and immunosuppressants is needed to prevent further progression, although the exact treatment regimen has not been rigorously studied in NSVN. Consultation with neurology or rheumatology is needed on an urgent basis. Further research is needed into optimal treatment regimens and mechanisms of injury.

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